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Original article

Predicting the need for adaptive radiotherapy in head and neck cancer

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ABSTRACT

Background and purpose: Adaptive radiotherapy (ART) can account for the dosimetric impact of anatomical change in head and neck cancer patients; however it can be resource intensive. Consequently, it is imperative that patients likely to require ART are identified. The purpose of this study was to find predictive factors that identify oropharyngeal squamous cell carcinoma (OPC) and nasopharyngeal carcinoma (NPC) patients more likely to need ART.
Materials and methods: One hundred and ten patients with OPC or NPC were analysed. Patient demographics and tumour characteristics were compared between patients who were replanned and those that were not. Factors found to be significant were included in logistic regression models. Risk profiles were developed from these models. A dosimetric analysis was performed.
Results: Nodal disease stage, pre-treatment largest involved node size, diagnosis and initial weight (categorised in 2 groups) were identified as significant for inclusion in the model. Two models were found to be significant ($p = 0.001$), correctly classifying 98.2% and 96.1% of patients respectively. Three ART risk profiles were developed.
Conclusion: Predictive factors identifying OPC or NPC patients more likely to require ART were reported. A risk profile approach could facilitate the effective implementation of ART into radiotherapy departments through forward planning and appropriate resource allocation.

Highly conformal, modulated techniques, such as intensity modulated radiation therapy (IMRT), helical IMRT (Tomotherapy) and volumetric modulated arc therapy (VMAT) are considered the standard radiotherapy techniques for the treatment of head and neck squamous cell carcinomas (HNSCC) [1–3]. These techniques enable delivery of high radiation doses to tumour volumes whilst minimising dose to surrounding structures with resultant reduction in toxicities experienced by patients [4]. However, geometric and anatomical changes that can occur over a treatment course may limit the benefits associated with these highly conformal techniques and should be considered when developing appropriate treatment approaches [2]. Anatomical changes can be attributed to a number of factors including shrinkage of tumour and nodal volumes, changes in tumour position and weight loss [5,6]. Various adaptive radiotherapy (ART) techniques have been evaluated to assess their effectiveness in addressing this issue however the ART process can be resource intensive on departments with replanning procedures requiring both additional use of planning equipment and staff time [6,7]. Consequently, it is imperative that patients who are likely to require ART are properly identified. This will facilitate the effective implementation of ART into radiotherapy departments by forward planning, resulting in gains in efficiency and appropriate allocation of departmental resources. ART in this context refers to the generation of a new radiotherapy plan based on imaging performed during a patient's treatment course that accounts for anatomical changes.

The majority of studies have primarily investigated factors that determine the requirement for ART whilst a patient is undergoing treatment. There are little published data on identifying factors that could predict the need for ART prior to the commencement of treatment. As patient selection for ART can be subjective, the focus of this study was to identify characteristics that pre-dispose patients to being more likely to require ART. Consequently, the primary aim of this project was to find predictive factors that identify oropharyngeal squamous cell carcinoma (OPC) and nasopharyngeal carcinoma (NPC) patients more likely to need ART. These predictive factors would be used to refine a risk profile approach previously developed. OPC and NPC were chosen as they both commonly

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present with nodal involvement, have a high rate of viral association (Human Papillomavirus (HPV) with OPC and Epstein Barr Virus (EBV) with NPC) and respond well to radiotherapy treatment.

Materials and methods

Patients

Between October 2013 and December 2014, 110 patients were recruited from three tertiary radiotherapy departments in Brisbane, Australia to join a prospective cohort study. This study was approved by the Princess Alexandra Hospital and Royal Brisbane and Women's Hospital Human Research Ethics Committees. Informed consent was obtained. Eligibility criteria included: histologically confirmed NPC or OPC, or metastatic cervical nodal disease of unknown primary suspected of arising from either the oropharynx or nasopharynx; absence of distant metastatic disease; treatment with radical radiotherapy with any IMRT technique including rotational arc or helical radiation therapy techniques; a radiation prescription dose of $\geqslant$50 Gy and with or without concurrent chemotherapy. Patients were excluded: if it was unknown whether their disease was virally associated or not; if they had undergone definitive resection of the primary tumour, and/or a neck dissection; if they were treated with a three-dimensional conformal radiotherapy technique and if there was an inability to spare at least one parotid gland (i.e. unable to achieve a mean parotid dose of $\leqslant$26 Gy [8] – 33 Gy [9]). Patient demographics, tumour characteristics (including pre-treatment size of the dominant node) and treatment details were recorded. Nodal size data were collected from each patient's diagnosis and staging information.

Treatment planning

All patients were positioned supine, immobilised in a thermoplastic mask covering the head and shoulder region. Patients underwent computed tomography (CT) simulation procedures according to standard departmental protocol and all CT scans were obtained using a helical CT scanner with 3 mm slice spacing. Intravenous (IV) contrast was not used for CT scanning as all patients had a positron emission tomography (PET)/CT fused with the planning CT for volume definition. Magnetic resonance imaging (MRI) scans were fused as appropriate with the planning CT scan to aid in target delineation. Target volumes were contoured according to the department's standard protocol.

ART management

Re-CT

Consented patients were allocated to one of three ART risk profiles primarily based on the pre-treatment size of their largest involved node, as previously described [10]. These risk profiles indicated which patients would have a second planning computed tomography (CT) scan (re-CT) booked prior to treatment commencement at fraction 15. Patients had a daily, pre-treatment cone beam CT (CBCT) or megavoltage CT (MVCT) scan taken. This scan was used during the treatment session to correctly align the isocentre. Scans were reviewed on a weekly basis by one of four Radiation Therapists to assess the need for the patient to undergo a re-CT for ART purposes. For all patients, a re-CT was performed if the difference between the planning scan and the CBCT was greater than 1 cm at any point of the patient's external contour within the treatment area. The only circumstance where a re-CT was not required was if the patient had seven fractions or less remaining in their treatment.

If a difference greater than 1 cm was noted for a patient receiving Tomotherapy, the original plan was re-calculated on the MVCT to make an initial assessment of the dosimetric impact of the anatomical change. On plan review, if the Radiation Oncologist considered the dosimetric impact to be clinically significant, a re-CT was performed. A flow chart outlining the study procedure is demonstrated in Supplementary Fig. 1.

Assessment for need of replan

For all patients that had a re-CT, the original CT and the re-CT were fused using rigid registration according to the region of interest specified by the Radiation Oncologist to assess the requirement for a new treatment plan (replan). The original plan was translated to the re-CT dataset and calculated using the original monitor units (MU). This method is similar to the hybrid technique described by Hansen et al. [6]. The treating Radiation Oncologist assessed the image registration and any volumetric deformations or positional shifts of target or organ at risk (OAR) structures and reviewed the plan through both visual inspection and evaluation of the dose volume histogram (DVH). Nodal gross tumour volumes (GTV-n), serial OAR and parotid glands were re-contoured. The decision to generate a replan was at the discretion of the treating Radiation Oncologist. Factors influencing a Radiation Oncologist's decision to replan included critical OAR, such as the spinal cord or optic structures, receiving dose above the accepted tolerance level and inadequate target volume coverage.

Doses received by the GTV-n, non-target tissue (NTT), spinal cord, brainstem and parotid glands were recorded from both the original plan and the delivered dose plan to assess dosimetric impact.

Replan

If a replan was necessary, target and OAR structures were re-contoured as required on the re-CT and a new plan generated. The aim of the new plan was to achieve at least comparable target volume coverage and OAR doses to the original plan.

Statistics

Patients who required a replan were compared with those that did not to identify common characteristics among the replan group. A three-stage approach was taken to the statistical analyses. For the first step, univariate and multivariate analyses were used including Chi squared [11] and Mann–Whitney [12] tests to compare various factors between the two groups. Comparison of dosimetric factors was conducted between the original treatment plan and the delivered dose using the Wilcoxon matched-pairs signed-ranks test. These tests were used as the data were not normally distributed. Tested factors included gender, age, diagnosis, disease stage, viral status, initial weight and initial size of the pre-treatment dominant node. A *p*-value of $\leqslant$0.05 was considered statistically significant. For the second stage logistic regression was used to model the relationship between the categorical outcome and explanatory variables. The explanatory variables used were determined in stage one. Logistic regression was used as the outcome being investigated was binary (i.e. replan). In the regression analyses, the binary response variable was the requirement for a replan and a *p*-value of $p \leqslant 0.05$ was considered to be statistically significant. Data were analysed using the Stata (version 12.1, StataCorp LP, Texas, USA) program. For the third stage, classification and regression trees (CART) were used to identify interacting relationships between explanatory variables and the categorical response variable. Only the identified explanatory variables were included in the CART analysis. CART analysis was performed in RStudio version 0.98.110 [13] using the rpart.plot package [14].

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